Rh Factor

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One major cause of Erythroblastosis fetalis or Hemolytic Disease of the Newborn (HDN) is Rhesus (Rh) incompatibility. Symptoms of HDN caused by the Rh factor (RhHDN) include jaundice, anemia, erythroblastosis, enlarged liver and spleen, and hydrops fetalis. This life threatening disease led to an explosion of research in the field of hematology, discovery of the Rh factor, and prevention of the disease.

The symptoms of HDN were documented hundreds of years ago, but doctors at the time did not realize that the symptoms had a common cause. The first case of HDN was documented in 1609 by a French midwife when a set of twins was born. One twin was stillborn and the other died from severe jaundice after birth (Gabbe). Such sudden, tragic deaths piqued the interest of scientists and the search for the cause of fetus and infant deaths began. In 1910 Schriddle was one of the first doctors to suggest that there appeared to be a link between the symptoms of edema and abnormal erythrocyte formation. It was discovered that the erythrocytes were being destroyed somehow, a symptom that became known as erythroblastosis. Rautman coined the term erythroblastosis in 1912 (Taylor, 1). In 1932, Diamond became the first doctor to recognize that the symptoms of edema, anemia, and jaundice were all symptoms of the same disease (Gabbe). Discovering the many symptoms of one disease, HDN, led to further research in hematology. Darrow was the first to hypothesize that the numerous symptoms of HDN were due to an immune reaction to an antigen in 1938. Levine and Stetson reported a case in which a woman had a reaction when transfused with her husband's blood. The strange thing was that the blood she received matched her blood type (Taylor 2). Alexander Wiener and Karl Landsteiner discovered the reason for such a transfusion reaction in 1940. They were conducting an experiment in 1937 in which they immunized guinea pigs and rabbits with blood from rhesus monkeys. Then they mixed the resulting antiserum with human blood and found that 85% of the blood samples agglutinated, clumped together (Levine 4-5). Landsteiner and Wiener's experiment discovered the Rhesus (Rh) factor, which was later found to be a major cause of HDN.

The Rh factor refers to an antigen found on red blood cells. There are five Rh antigens: D, C, E, c, and e. The genes for Rh factor have eight possible haplotypes made up of 3 alleles: Dce, DCe, DcE, DCE, dce, dCe, dcE, and dCE. The d allele refers to the absence of the D antigen. The D antigen is responsible for most cases of Rh factor HDN (RhHDN) (McPherson and Pincus). People that have the D antigen are said to be Rh+ and those without the antigen are Rh- (Derrickson and Tortora 369). Rh+ is a dominate trait, meaning two recessive genes are required for someone to be Rh-. Eighty-five percent of Caucasians, 95.5 percent of African Americans, and nearly 100 percent of American Indians, Chinese, and Japanese are Rh+ (Levine 5-7). Therefore, Caucasians are most affected by Rh incompatibility. When Rh+ blood comes into contact with Rh- blood, powerful immune responses take place.

Erythroblastosis fetalis occurs when an Rh+ fetus is attacked by its Rh- mother's immune system. However, the immune response typically does not attack the fetus of a woman's first pregnancy. During birth, abortion, or problems during pregnancy, the baby's blood can leak through the placenta and into the mother's bloodstream. When the Rh+ blood of the fetus comes into contact with the Rh- mother's blood, an antibody-mediated immune response occurs in the mother's body. B cells ingest the Rh antigens by phagocytosis. Digestive enzymes break down the antigen into peptide fragments while major histocompatibility complexes (MHCs) are produced and packaged in vesicles within the B cell. The vesicle containing the MHC fuses with the vesicle containing the peptide fragments. The peptide fragments and MHC molecules bind to each other to form antigen-MHC complexes. Then the vesicle releases the antigen-MHC complexes so they can insert into the plasma membrane of the B cell. Next, helper T cells bind to the antigen-MHC complex and secrete proteins that activate the B cells. The B cells proliferate and differentiate to form plasma cells, which secrete anti-Rh antibodies, and memory B cells which help make a swift attack if the immune system encounters the D antigens again. The antibodies attack and destroy the Rh antigens (Derrickson and Tortora 448-451). The mother's first encounter with the Rh-antigens causes the production of immunoglobulin (Ig) M, a class of antibodies (Abbas). Since IgM is unable to cross the placenta (Derrickson and Tortora 444), HDN typically does not occur in the firstborn.

Subsequent invasions of a fetus's Rh antigens in the mother's body will elicit a stronger, faster immune response due to the increase of memory B cells. Repeated exposure to the D antigen produces IgG, a class of antibodies that can cross the placenta and attack the fetus's red blood cells (RBCs) (Abbas et al.).

Rh incompatibility can lead to many problems for fetuses and infants such as anemia, jaundice and edema due to the destruction of erythrocytes (Behrman et al.). Erythrocytes are mature blood cells and they play a major role in gas exchange for the body. When the oxygen levels within the body drop, the kidneys produce erythropoietin, which stimulates the production of RBC (Derrickson and Tortora, 362). However, the fetus is unable to produce enough RBCs to combat the destruction of its RBCs by the mother's antibodies and develops the symptom known as anemia. Blood smears from infants suffering from RhHDN show a large number of nucleated red cells and reticulocytes (Snelling 47). Some of the RBCs that are actually able to survive the immune response become spherocytes. These cells swell, forming round cells, rather than concave cells (Dameshek 44-45). Neither the immature RBCs nor the spherocytes are capable of carrying oxygen, making them useless. Since the oxygen levels in the newborn's body continue to drop, the kidneys keep cranking out more erythropoietin and RBCs continue to be produced in the bone marrow, spleen, and liver. The high production of RBCs leads to a buildup of fluid, causing these sites to swell (Abbas et al.). The large amounts of fluid also accumulate in skin, placenta, amniotic fluid, and body cavities such as the pleural, pericardial, and peritoneal cavities. Fluid in two or more of these areas is called hydrops fetalis. Fluid in the lungs of a fetus can cause asphyxia at birth. The extra fluid in body cavities can also put pressure on the organs and cause heart failure. Severe cases of hydrops fetalis result in reduced production of platelets, causing hemorrhaging, and increased pressure on the right side of the heart, causing heart failure (Behrman et al.).

After birth, an infant can encounter liver problems such as jaundice as a result of RhHDN. When a RBC is destroyed by the anti-Rh antibodies, macrophages from the spleen, liver, and bone marrow engulf the destroyed RBCs through phagocytosis. The hemoglobin is split into heme, iron, and globulin. Globulin and iron are recycled for RBC production and stored in the liver and spleen. The iron-free heme is converted into a green pigment called biliverdin and then into a yellow-orange pigment called bilirubin (Derrickson and Tortora 361-362). The bilirubin is unconjugated in fetuses. After birth, the infant's body tries to conjugate the bilirubin and get rid of it (Behrman et al.). In a normal functioning body, the liver secretes the bilirubin as bile into the small intestine. The bile winds through the small intestine and enters the large intestine where bacteria convert it into urobilinogen. Finally, the urobilinogen is either converted to stercobilin and excreted in feces or converted to urobilin and excreted in urine (Derrickson and Tortora 362). However, this process of excreting bilirubin is unsuccessful in many infants who battle Rh incompatibility. The infant's body is overwhelmed by the large amounts of unconjugated bilirubin. Jaundice can be observed as yellowing of the skin caused by the accumulation of the bilirubin under the skin. Further problems can occur as a result of jaundice if the bilirubin travels to the brain through the blood. Unconjugated bilirubin is a nonpolar, lipid-soluble substance; therefore, it can bind to lipids in the brain and pass through the blood-brain barrier. Deposits of bilirubin in the basal ganglia and brain stem nuclei result in damage to the central nervous system. This is called kernicterus (Abbas et al.).

Due to the many life threatening symptoms of RhHDN, treatment focuses on immediate treatment of the baby before and after birth. One treatment for RhHDN is a blood transfusion which helps with the symptoms of severe anemia. Exsanguination is a procedure that removes the baby's Rh+ blood while replacing it with Rh- blood at the same time. By removing and replacing the

blood at the same time, shock is prevented. It is also important that the infant receives Rh- blood, not Rh+ blood as was once hypothesized. If the infant receives Rh+ blood, the anti-Rh antibodies will continue to attack the erythrocytes of the newly transfused blood. There is no immune reaction to the Rh- negative blood, allowing the infant to have mature, functioning RBCs (Wallerstein 170-173). Exsanguination is a transfusion that occurs after a baby is delivered. Fetuses can also receive blood transfusion. This risky procedure is used if an ultrasound shows signs of severe hydrops fetalis. The intravascular fetal transfusion gives the fetus Rh- blood via the umbilical cord. The procedure has an 89 percent survival rate. Complications of this potentially risky procedure include preterm delivery, infection, fetal distress, and perinatal death (Behrman et al.).

Jaundice is another potentially life threatening symptom of RhHDN. It is treated by phototherapy, the use of high intensity visible light from fluorescent lamps. The light causes photochemical reactions that change the unconjugated bilirubin to another isomer that the body can pass without being conjugated. Phototherapy also reduces the number of repeated blood transfusions for severe cases of jaundice (Abbas et al.).

Newer, preventative treatments for RhHDN focus on preventing RhD sensitization in the Rh- mother. John Gorman and Vincent Freda proposed using Rh immune globulin (RhoGAM) to prevent women from being sensitized to the RhD antigen in the early 1960s (Gabbe). William Pollack made an intramuscular injection called RhoGAM. The injection was made from human plasma that contained anti-D antibodies (Gabbe). Gorman and Vincent's research showed that RhoGAM had 100% success rate in preventing sensitization to the Rh antigen in human beings. It was also successful in preventing sensitization in Rh- women when it was used after they delivered an Rh+ baby. RhoGAM destroys any Rh antigens that may enter the mother's body, stopping immune responses since there is nothing left to attack. RhoGAM was accepted for clinical use in 1968 by the Division of Biologics Standards of the National Institutes of Health. In 1970, the American College of Obstetricians and Gynecologists proposed the use of RhoGAM at twenty-eight to twenty-nine weeks gestation in addition to its use postpartum (Gabbe). The number of cases of RhHDN per number of births dropped from 40.5 in 1970 to 14.3 cases per 10,000 total births in 1979 (Adams 1031). Finally, the Food and Drug Administration approved its use in 1981 (Gabbe). The RhoGAM is now used at twenty-eight weeks gestation and within seventy-two hours after delivery or abortions in Rh- mothers who are carrying Rh+ babies (Abbas et al.). As a result, RhoGAM has reduced the risk of Rh- mothers producing anti-Rh antibodies to less than 1 percent (Behrman et al.). Research is being done now to make a vaccine like RhoGAM that can be produced from synthetic material instead of human plasma (Gabbe).

Thanks to Landsteiner and Wiener, Rh incompatibility and its symptoms are better understood. It is amazing what the immune system can do. One expects a mother's body to care and nurture a fetus, but with exposure to the Rh antigen, an Rh- mother's immune system can turn against her fetus. Jaundice, anemia, and fetal hydrops are some of the symptoms that result from the vicious attack of the anti-Rh antibodies. With new technology, the risk of having a baby with RhHDN is greatly reduced. Treatments such as phototherapy and blood transfusions help alleviate some of the life threatening symptoms of RhHDN. RhoGAM prevents the immune response of Rh incompatibility, and thereby, prevents RhHDN from occurring. A once terrifying disease is for the most part under control due to the better understanding of Rh incompatibility and immune responses in the human body.

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